

Important Advances in Clinical Medicine

Epitomes of Progress—Anesthesiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in anesthesiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in anesthesiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Anesthesiology of the California Medical Association and the summaries were prepared under its direction.

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Dantrolene: Specific Drug Therapy for Malignant Hyperthermia

MALIGNANT HYPERTHERMIA is a fulminant hypermetabolic crisis induced by anesthetic trigger agents in genetically susceptible persons. The full-blown syndrome, with tachycardia, cardiac dysrhythmias, unstable blood pressure, fever, rigidity, hypoxemia, lactic acidosis, hyperkalemia and myoglobinemia, has a mortality of 60 percent. This syndrome has been reported in patients ranging in age from 3 months to 70 years.

Malignant hyperthermia results from a defect of membrane calcium transfer in skeletal muscle. The sarcoplasmic reticulum, in response to a triggering stimulus, releases an abnormally large amount of calcium because of abnormal "leakiness," or by its inability to reaccumulate calcium from the myoplasm back into intracellular storage sites. Excess myoplasmic calcium produces an abnormal amplification of excitation-contraction coupling. The resulting hypermetabolism and continued contraction of skeletal muscle generate heat, exhaust adenosine triphosphate stores, uncouple mitochondrial oxidative phosphorylation, and lead to further cellular and membrane derangements.

Until recently the treatment of malignant hyperthermia consisted only of supportive measures—discontinuance of anesthesia, hyperventilation with 100 percent oxygen, sodium bicarbonate for metabolic acidosis, procainamide for cardiac dysrhythmias, cooling, diuretics to prevent myoglobin from precipitating in the renal tubules, and treatment of hyperkalemia. Although it may restore blood gas and other laboratory values, supportive therapy does not alter the underlying and continuing pathological defect.

Dantrolene sodium, which acts to prevent excessive release of intracellular calcium, is one of several hydantoin synthetized by Snyder and associates in 1967 that proved to have muscle relaxant properties. Extensively investigated, dantrolene is known to act directly on skeletal muscle but has no effect on smooth and cardiac muscle. It does not affect neuromuscular transmission or electrically excitable surface cell membranes. Van Winkle showed that dantrolene is pharmacologically active within the sarcotubular system where it suppresses the release of calcium. It has proved effective in the treatment and reversal of malignant hyperthermia in both swine and humans.

Dantrolene is not a substitute for aggressive, supportive therapy—it is a specific adjunct to